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SIMULTANEOUS BILATERAL REAL-TIME 3-D TRANSCRANIAL ULTRASOUND IMAGING AT 1 MHZ THROUGH POOR ACOUSTIC WINDOWS

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Abstract

Ultrasound imaging has been proposed as a rapid, portable alternative imaging modality to examine stroke patients in pre-hospital or emergency room settings. However, in performing transcranial ultrasound examinations, 8%–29% of patients in a general population may present with window failure, in which case it is not possible to acquire clinically useful sonographic information through the temporal bone acoustic window. In this work, we describe the technical considerations, design and fabrication of low-frequency (1.2 MHz), large aperture (25.3 mm) sparse matrix array transducers for 3-D imaging in the event of window failure. These transducers are integrated into a system for real-time 3-D bilateral transcranial imaging—the ultrasound brain helmet—and color flow imaging capabilities at 1.2 MHz are directly compared with arrays operating at 1.8 MHz in a flow phantom with attenuation comparable to the *in vivo* case. Contrast-enhanced imaging allowed visualization of arteries of the Circle of Willis in 5 of 5 subjects and 8 of 10 sides of the head despite probe placement outside of the acoustic window. Results suggest that this type of transducer may allow acquisition of useful images either in individuals with poor windows or outside of the temporal acoustic window in the field.

Keywords

Transcranial; Temporal acoustic window; Real-time 3-D ultrasound; Contrast-enhanced

INTRODUCTION

As the second-leading cause of death in developed nations, stroke constitutes a significant public health concern (World Health Organization 2008). In the United States, stroke constitutes 17% of overall national health spending (Heidenreich et al. 2011). At present, stroke diagnosis commonly relies on imaging with X-ray computed tomography (CT) to rule out hemorrhage and enable administration of thrombolytics (Smith et al. 2003; Adams et al. 2005). Ischemic stroke comprises approximately 87% of all stroke cases (Roger et al. 2011). Of these, 68% affect the anterior circulation, supplied by the left and right internal carotid arteries, with 96% of these occlusions occurring in the middle cerebral arteries (Bogousslavsky et al. 1988). Given an aging population and the high incidence of stroke in developed nations (Carandang et al. 2006; Tobias et al. 2007; Hallstrom et al. 2008;

Heuschmann et al. 2008), providing rapid diagnostic imaging of stroke is essential. If a stroke can be determined to arise from the presence of a thrombus or embolus and hemorrhage can be ruled out within a specified time window—currently 4.5 h in the United States (Davis and Donnan 2009; Del Zoppo et al. 2009)—tissue plasminogen activator (tPA) can be administered intravenously to lyse the thrombus, decreasing recovery times and improving patients' functional outcomes (Hacke et al. 1995). Approximately 50% of patients receiving tPA experience full recovery within 3 mo (NINDS rt-PA Stroke Study Group 1995).

In recent years, investigators have explored using transcranial ultrasound imaging to fill a niche as a portable, inexpensive approach to stroke imaging, the feasibility of which has been demonstrated in various pre-hospital settings including ambulances, emergency helicopters and in remote environments (Holscher et al. 2008; Bowman 2010; Hoyer et al. 2010; Chenaitia et al. 2011; Wilson et al. 2011; Schlachetzki et al. 2012). By reducing the time to diagnosis and increasing confidence in the diagnosis, prehospital imaging might increase the number of eligible patients receiving tPA, currently at 1%–7% (NINDS rt-PA Stroke Study Group 1995; Katzan et al. 2000; Koennecke et al. 2001). Three-dimensional ultrasound is particularly well-suited to emergency medicine, because an operator with limited training has a greater likelihood of capturing clinically useful information within a 3-D volume than within a single 1-D scan or 2-D slice. In the hospital setting, 3-D ultrasound has been cited as a potentially faster and clinically acceptable alternative to X-ray for examining blood flow in intracranial collateral arteries (Wessels et al. 2004).

However, the viability of pre-hospital transcranial ultrasound imaging is dependent on the ability of the operators—emergency medical personnel—in acquiring diagnostically useful images. Researchers at the University of California-San Diego and Regensburg University have recently demonstrated proof-of-concept use of portable 2-D ultrasound in visualizing intracranial vessels in real-time either at the site of the emergency or during patient transport by ambulance or helicopter (Holscher et al. 2008). A follow-up publication reported a sensitivity of 90% and a specificity of 98% in detecting MCA occlusions in the field (Schlachetzki et al. 2012). This group is currently attempting to train paramedics to perform such exams (Holscher 2012); the outcome of this training program will provide an important indicator as to the feasibility of performing transcranial ultrasound examinations by operators with limited training. Manufacturers of ultrasound scanners have also investigated reducing the operator dependence of ultrasound scans in various anatomical regions, including designing conformal arrays for abdominal imaging (Daft 2010), developing an automated breast scanner (Porter and Seck 2009) and providing on-screen feedback of probe placement in transcranial imaging (Vignon et al. 2009). If emergency medical personnel could acquire diagnostically useful images in the field, those images might be transferred to the stroke team at the hospital *via* telemedicine, as has recently been demonstrated with a portable CT scanner and a telemedicine unit (Walter et al. 2012). However, at this time it is unknown whether transcranial ultrasound scans may be reliably performed by individuals with limited training.

Additionally, transcranial ultrasound faces physical challenges in overcoming the attenuation and aberration introduced by the skull. Aaslid et al. first presented the temporal acoustic window as a thinner, more homogeneous region of the temporal bone relative to the rest of the skull through which one-dimensional transcranial Doppler (1-D TCD) examinations could be performed (Aaslid et al. 1982). It was later described as a roughly circular region 2–3 cm in diameter having a thickness of 2–3 mm (Becker and Griewing 1998; Furuhashi 1998). The decreased attenuation within the window results from structural variation: the skull within the window consists of an inner and an outer table of compact bone with little or no trabecular bone between them (Becker and Griewing 1998).

Grolimund reported a one-way mean attenuation of 7 dB due to transmitting through the window at 2 MHz (Grolimund 1986).

However, the simplified view of the temporal acoustic window as a several centimeter-wide region free of trabeculae does not always hold; in many patients a suitable imaging window may not be found. Temporal bone window failure rates in the range of 8% to 29% have been reported (Table 1) (Hashimoto et al. 1992; Seidel et al. 1995; Baumgartner et al. 1997; Marinoni et al. 1997; Postert et al. 1997; Gahn et al. 2000; Krejza et al. 2007; Wijnhoud et al. 2008). Of individuals with window failure, 39% had bilateral window failure in a study of 624 subjects (Marinoni et al. 1997). Previous studies of window failure were performed in the 2–3 MHz range; none used 3-D ultrasound. While microbubble contrast-enhancement may reduce window failure rates, it does not eliminate window failure in all patients (Baumgartner et al. 1997; Postert et al. 1997; Gahn et al. 2000). Of particular interest is the study of Wijnhoud et al., in which a window failure rate of 18% was found in 182 subjects having a transient ischemic attack or minor ischemic stroke, thus investigating window failure in a population representative of stroke patients. Results of this study indicate that absence of window failure may be predicted by three factors: skull thickness, age and gender.

In previous work, we demonstrated simultaneous bilateral real-time 3-D transcranial ultrasound, the ultrasound brain helmet (Smith et al. 2009). More recently, we described the ability to simultaneously acquire two 3-D transcranial volumes from either side of the head (Fig. 1a) and fuse these volumes into a single 3-D visualization offline both with and without contrast agent (Lindsey et al. 2011). In real-time, two orthogonal imaging planes are displayed from each transducer (Fig. 1b). This scanning configuration provides advantages by decreasing the scan depth required for a single transducer, allowing for assessment of asymmetry between blood flow on the left and right sides of the head (Kenton et al. 1997), and providing the possibility of overcoming a single unfavorable temporal acoustic window. In Figure 2, we present two simultaneously-acquired bilateral real-time 3-D transcranial ultrasound volumes acquired with this system during a previous study according to an IRB-approved protocol (Lindsey et al. 2011). These volume renderings show results of scanning *via* favorable and less favorable windows in two different adult female subjects scanned with micro-bubble contrast enhancement at 1.8 MHz. In the new study presented in this article, we will attempt to avoid results such as the window failure case (Fig. 2b) by scanning with custom-designed, lower frequency matrix arrays. While reducing transmit frequency (alternatively, increasing wavelength) produces a proportional increase in spatial resolution, in this work we will maintain constant imaging resolution by concomitantly increasing the size of the aperture in the designed arrays. In the expression for lateral resolution $\lambda z/D$, D is increased to offset the increase in λ .

While presenting window failure rate as a single number as in Table 1 provides a starting point for understanding the prevalence of this problem, it is also an over-simplification in that results are averaged over gender, age groups and ethnic groups. The success rate of trans-temporal imaging remains low in certain populations, particularly elderly women and non-whites (Grolimund et al. 1987; Bruno et al. 1988; Eden 1988; Halsey 1990; Fujioka and Douville 1992; Hashimoto et al. 1992; Itoh et al. 1993; Comerota et al. 1995; Baumgartner et al. 1997). Halsey found window failure rates of 13% in white males, 18% in white females, 23% in black males and 50% in black females at 2.0 MHz (Halsey 1990). Alternatively, Hoksbergen reported failure rates of 1% in white men and 23% in white women over age 60 (Hoksbergen et al. 1999). In a Japanese population, Hashimoto reported a significant increase in window failure rates beginning at age 50, especially in women (Hashimoto et al. 1992). Hyperostosis—thickening of the skull's inner table—has been proposed as a possible explanation for window failure in elderly women (Eden 1988).

Hyperostosis has been observed in 6% to 12% of adult women of all ages (as compared with only 1% of men) (Moore and Carr 1952; Gegick et al. 1973), and in 50% of women over the age of 60 at time of death (Henschen 1939).

The groups having the highest incidence of window failure are some of the same populations at greatest risk for stroke. In the United States, the incidence of stroke among African-Americans is almost double that of white Americans, and twice as many African-Americans who have a stroke die from it compared to white Americans (NINDS 2004). Women are less at risk for stroke than men, although on average women have strokes at a greater age than men and are more likely to die (NINDS 2004).

Given an uncertain rate of window failure in these at-risk populations varying from perhaps 20% to 50%, we propose performing 3-D diagnostic transcranial ultrasound at lower frequencies, near 1 MHz. For most diagnostic equipment—either imaging or non-imaging transcranial Doppler—this would require new transducers capable of operating at lower frequencies. In this article, we describe the design, fabrication and testing of a new prototype 3-D bilateral imaging device with matrix array transducers operating at 1.2 MHz with the goal of performing transcranial imaging either outside of the window or in patients exhibiting window failure.

Previous efforts have attempted to address the effects of poor temporal acoustic windows by using the other window (Marinoni et al. 1997) or by finding the optimal probe placement (Vignon et al. 2009). Other attempts at overcoming the skull in ultrasound imaging include inducing shear-mode conversions at the soft tissue-skull interfaces (Clement et al. 2004; Yousefi et al. 2009) and various phase aberration correction techniques including multi-lag least squares approaches (Flax and O'Donnell 1988; Liu and Waag 1994; Ivancevich et al. 2008; Ivancevich et al. 2009) and spatiotemporal inverse filtering (Aubry et al. 2001; Tanter et al. 2001; Vignon et al. 2006). Most recently, our own group has described bilateral 3-D phase aberration correction of the skull bone using pitch-catch measurements (Lindsey and Smith). However, in the present article, we will focus on attenuation rather than aberration. It is worth noting that at lower frequencies, the effect of aberration is also diminished, as the root-mean-square amplitude—or “strength”—of the aberrator constitutes a smaller fraction of a wavelength at 1 MHz relative to 2 MHz (Smith 1975; Davros et al. 1985).

Previous probe designs for transcranial ultrasound include a low-frequency 1-D TCD probe (Klotzsch et al. 1998; Cullinane and Markus 2001), therapeutic arrays for high-intensity focused ultrasound (Clement et al. 2000; Hynynen et al. 2004; Hynynen and Clement 2007), a combined probe for imaging and thrombolysis (Azuma et al. 2010; Shimizu et al. 2012) and a 128-element, 750 kHz linear array (Meral and Clement 2010). Outside of our own previous work, no known previous attempts at matrix arrays for transcranial imaging have been made.

MATERIALS AND METHODS

Scanning system

Bilateral imaging in this work was performed using the Volumetrics Model 1 scanner (Volumetrics Medical Imaging, Durham, NC), modified as previously described (Lindsey et al. 2011). Offline fusion of simultaneously-acquired imaging volumes is performed by maximizing correlation in the frequency domain (Reddy and Chatterji 1996), then summing the two spatially-registered volumes in place. Four slices from two probes are displayed in real-time: one azimuth and one elevation slice from each transducer, corresponding to coronal and transverse planes in transtemporal imaging (Fig. 1b). The operator uses a trackball control to select four slices (any two from each transducer) for real-time display.

Lateral line separation is in 1.2° azimuth and 2.4° in elevation. Typical range gate resolution is 200 gates per line, so for Doppler gates with an extent of 6 cm in depth, Doppler spatial resolution is 0.3 mm. However, the angular resolution is limited by the transducer angular resolution of 3.1° , discussed in the “Transducer design” section (Fig. 4). The minimum detectable velocity is determined by the wall filter and is 11 cm/s (172 Hz). Figures in this paper present the magnitude of the Doppler data.

Frequency and SNR considerations

In transcranial ultrasound imaging, Hölscher et al. have used a 1 MHz transmit pulse in the development of a harmonic contrast-enhanced transcranial imaging technique, though the transducer arrays used in this work were 1-D and 1.5D arrays centered at 2.5 MHz (Holscher et al. 2005). Investigations in transcranial therapeutic ultrasound (Ammi et al. 2008) and non-imaging TCD (Klotzsch et al. 1998) also support decreasing transmit frequency from greater than 2 MHz to the 1 to 2 MHz range as a means of overcoming insufficient bone windows. Seeking theoretical basis for these indications in the literature, we have examined a simple model for answering the question of which frequency is best for transcranial ultrasound imaging.

For the continuous wave case, a design frequency (f) for maximizing the backscattered echo in an attenuating medium for a given depth (R) and attenuation (β) can be determined by using the product of the expression for frequency-dependent attenuation and the square of frequency (Rayleigh scattering is assumed) (Reid and Shung 1979). The derivative of this product is then set to zero, yielding the final result in eqn (1b):

$$P = P_0 \exp(-2(\beta_1 R_1 + \beta_2 R_2) f) f^2 \quad (1a)$$

$$f = \frac{1}{\beta_1 R_1 + \beta_2 R_2} \quad (1b)$$

Using a conversion factor of 0.1151 Nepers/dB, in the case of transcranial imaging with $R_1 = 2$ mm of skull at $\beta_1 = 2.8$ dB/cm/MHz (White and Stevenson 1978) and $R_2 = 7$ cm of brain parenchyma (approximately to the midline) at $\beta_2 = 1.0$ dB/cm/MHz, eqn (1b) yields a design frequency of 1.1 MHz. Outside of the window ($R_1 = 4$ mm, $\beta_1 = 20$ dB/cm/MHz), the design equation produces a frequency of 0.6 MHz. This is far too low for our scanner, which cannot transmit below 1.2 MHz, and leads to serious concerns regarding the size and resolution of an array that can be reasonably built and coupled to a human head since a 0.6 MHz array would need to be twice as large as a 1.2 MHz array to maintain resolution. The inability to transmit below 1.2 MHz also precludes harmonic imaging with a transmit frequency of 0.6 MHz and a receive frequency of 1.2 MHz. While this is a simple calculation for the continuous wave case, this corroborates the view expressed by other investigators: a probe having a resonant frequency of approximately 1 MHz, which is lower than those commonly used, may be advantageous. While this simple model does not account for specular reflections, the frequency-dependence of such reflections is negligible when wavelengths are much smaller than the skull-soft tissue interface surface.

On the basis of data acquired from point target echoes in a water tank as a measure of electronic SNR, we estimated signal to noise ratio (SNR) for our system as a function of increasing skull thickness. This SNR was then two-way attenuated by 7 cm of soft tissue and 0.3 cm of skull inside the acoustic window versus 7 cm of soft tissue and 0.4 cm of skull outside of the window, while the signal amplitude was assumed to vary with frequency according to f^2 (Rayleigh scattering). The plots of SNR versus frequency (Fig. 3) indicate

that (1) SNR falls off very rapidly at 1.8 MHz outside of the window and (2) for reasonable skull thicknesses outside of the window, 1.2 MHz would be expected to significantly outperform 1.8 MHz, generally by at least 5 dB. Under these parameters, imaging outside the window at 1.8 MHz is not possible for skull thicknesses beyond 0.25 cm.

As previously noted, the ability to perform transcranial color flow imaging is of particular interest due to its potential diagnostic utility. Given the SNR of Figure 3, this signifies that (i) for our system, color flow imaging will be very difficult given that blood scattering generally lies 20–40 dB below tissue echoes (Jensen 1996), (ii) to successfully image blood flow from outside of the window, the design model should reflect color flow SNR rather than just echo SNR and (iii) although it is desirable to perform transcranial color flow imaging without contrast enhancement, the necessity of using microbubble contrast agent seems likely with this system. In light of (ii), we will briefly consider system color flow SNR.

Color flow SNR

While SNR considerations have been examined, Doppler imaging is of greatest interest for the proposed applications. Color Doppler SNR is largely determined by the operation of the stationary target canceller, or “wall” filter. The most common types of wall filters are the single- and double- delay-line cancellers, which remove stationary echoes by weighted subtraction of two or three successive lines of demodulated, digitized data. While efficient to implement, these filters also have zeros in their magnitude spectra which depend on the flow velocity and pulse repetition frequency (PRF) (Jensen 1996). In addition, because the wall filter cancels the highest-amplitude signals, the remaining blood flow signals suffer from low dynamic range since they occupy only the least significant bits during analog-to-digital conversion. Because of the complex relationship between echo and color flow SNR, the color flow imaging capabilities at the two frequencies will be directly compared experimentally.

Transducer design

In designing an approximately 1 MHz sparse 2-D array, the spatial dimensions of the 2.5 MHz aperture previously designed for transcranial imaging through the window (Lindsey et al. 2011) were scaled by approximately 2.5 to maintain resolution at the lower frequency. The resulting array has an element pitch of 0.725 mm and an aperture diameter of 25.3 mm (Fig. 4a). Simulations of the two-way beam for the 1 MHz array were produced using Field II (Fig. 4b, c, d) (Jensen and Svendsen 1992). –6 dB beam width for the unsteered response is 3.8×3.8 mm at a depth of 7 cm, an approximate measure of spatial resolution in the lateral dimensions. Cross talk is negligible and its effect on the beam has been ignored (*Transducer testing* section).

The proposed 2-D array acoustic stack—consisting of ground foil, PZT, flex circuit and acoustic backing—was simulated using the KLM model (PiezoCAD, Sonic Concepts, Bothell, WA) (Krimholtz et al. 1970; Desilets et al. 1978). The transducer was simulated with water at the front acoustic port, and additionally with the appropriate loads for imaging inside and outside of the temporal acoustic window using the attenuation values of White and Stevenson inside and outside of the window (White and Stevenson 1978). Electrical parameters were set to system values. Acoustic parameters for these simulations are given in Table 2. Transducer impulse response and the response to a 3 cycle, 1.2 MHz excitation waveform were simulated.

Transducer fabrication

The simulated transducer described in Figure 4 and Table 2 was built on a custom flexible multilayer circuit having a polyimide substrate, 5 μm -thick copper traces and 9 μm copper pads with ENIG (electroless nickel, immersion gold) finish, with pads arranged as in Figure 4a (Microconnex, Snoqualmie, WA). Total thickness of this flex circuit was 209 μm , or 0.13λ at 1 MHz. A $27 \times 27 \times 1.37$ mm piece of high dielectric constant PZT-5H (TRS Technologies, State College, PA) was bonded to the flex circuit by screen printing a silver-loaded anisotropic conductive epoxy (Chomerics, Woburn, MA) onto the back of the PZT. The bonded PZT was then diced using a programmable dicing saw (Disco DAD3220, Tokyo, Japan). A photograph of an array after dicing is shown in Figure 5. Kerf widths are approximately 90 μm . A ground foil was screen printed with conductive epoxy and bonded to the diced PZT, then the transducer was sealed. Finally, a lossy acoustic backing was cast and bonded to the back of the flex circuit. Two completed arrays were connected to a custom printed circuit board (PCSM/Moog Components, Galax, VA) via 300-pin connectors (Samtec BTH/BSH, New Albany, IN). This board then mates with the scanner front end.

Transducer testing

The following measurements were made in a water tank on fabricated arrays: pulse-echo sensitivity/bandwidth, 50 Ω insertion loss and crosstalk. Pulse-echo testing was performed on individual channels by positioning an aluminum block reflector as close as possible to the face of the transducer. The transducer was excited using a pulser-receiver (Panametrics 5073PR) and power amplifier (ENI 525). Results were viewed on an oscilloscope (Tektronix 744A) and on a spectrum analyzer (HP3588A) with the use of a stepless gate (Panametrics 5605A). Insertion loss testing was performed with a 50 Ω source transmitting a 5 cycle, 1 MHz pulse. Element yields were tested during fabrication using a complex impedance analyzer (HP4194A) and after connecting the transducer to the scanner using a 14-bit programmable acquisition board (Signatec PDA14, Corona, CA) to digitize single channel echoes from a point target.

Safety measurements

Measurements in this section were made using a calibrated membrane hydrophone (Sonic Tech, Hatboro, PA) in a water tank. The spatial location on the hydrophone giving the maximum response was positioned at the transducer focus (7 cm). Acoustic output measurements were made while scanning in spectral Doppler mode with the highest transmit power level to measure worst-case values.

Mechanical index (MI) is used to estimate the potential for mechanical bioeffects, although no adverse effects in humans have been reported due to exposure to diagnostic-level ultrasonic pressures (Abbott 1999). The threshold for cavitation is reduced in the presence of microbubble contrast agents, though contrast-enhanced color Doppler sonography at approved diagnostic output levels has not shown any signs of damaging brain tissue or opening the blood-brain barrier (Schlachetzki et al. 2002). FDA limit for MI is 1.9.

The cranial bone thermal index (TIC) is a measure of heating at the transducer-bone interface (Abbott 1999). There is no FDA limit for TIC, and it is infrequently reported in literature, though it is part of the output display standard (AIUM/NEMA 1998).

Phantom imaging

Phantom testing was conducted in a water tank with side-viewing silicone rubber panels with 5 mm diameter latex tubing passing through the center of the tank in a U-shape to mimic a blood vessel. Gravity-fed seltzer water was made to flow through the tubing at approximately 50 cm/s, similar to systolic flow velocity in the internal carotid artery ($66 \pm$

16 cm/s) (Valdúez et al. 2008). A 3 mm attenuator comprised of Wallgong absorbing rubber (Consumer Usage Labs, Parkville, MD) was placed in front of each transducer, producing two-way attenuation of 45.2 dB at 1.8 MHz and 32.9 dB at 1.2 MHz. This is similar to two-way *in vivo* attenuation outside of the temporal acoustic window, which is computed to be 43.2 dB at 1.8 MHz and 28.8 dB at 1.2 MHz (assuming 0.4 cm at 30 dB/cm/MHz) (White and Stevenson 1978; Ivancevich 2009). The rubber attenuators mimic the effects of *in vivo* attenuation, not reflections, although reflections due to mismatches in acoustic impedance may be assumed to be frequency-independent.

The 1.8 MHz arrays used in phantom and *in vivo* experiments are modified versions of the 2.3 MHz arrays used in the previous study (Lindsey et al. 2011). They were constructed using the same flex circuit as the 2.3 MHz array but PZT having a different thickness (760 μm for 1.8 MHz versus 600 μm for 2.3 MHz) so that their resonant frequency is 1.8 MHz and thus provides a fair comparison for the newly designed arrays operating at 1.2 MHz.

***In vivo* imaging**

As a surrogate for window failure, we scanned all subjects outside of their temporal acoustic windows by placing the probes above the pinnae of the ears, superior to the window by approximately 2 cm. In a pilot study, one of the authors (S.S.) scanned himself to provide *in vivo* comparison between dual flex transducers at 1.8 MHz and 1.2 MHz in a healthy 64-year-old male. This subject was first scanned at 1.2 MHz with the probes, described in the Methods section, placed superior to the temporal acoustic windows by approximately 2 cm. On-screen image quality was optimized by adjusting the overall gain and the time gain control. Next, the subject was scanned with 1.8 MHz probes fabricated as described previously (Lindsey et al. 2011), again optimizing on-screen image quality. Care was taken to position the probes in the same position on the skull and to acquire the same field of view as with the lower frequency arrays.

Five additional healthy subjects were then scanned with Definity (Lantheus Medical Imaging, North Billerica, MA) microbubble contrast agent enhancement only at 1.2 MHz after providing informed consent according to a protocol approved by the Institutional Review Board of Duke University. Because there was not time to change and reposition transducers or modify scanner settings after injection and each subject is limited to two doses of 10 $\mu\text{L/kg}$, these subjects were not scanned at 1.8 MHz. The five subjects consisted of 4 males, 1 female; 4 Caucasians and 1 African-American. Data for each subject were reviewed in offline 3-D renderings and in the scanner's orthogonal 3-D display to assess visibility of each of the following vessels: left and right internal carotid arteries, left and right middle cerebral arteries, left and right posterior cerebral arteries, and anterior carotid artery (treated as a single structure for identification purposes). The presence of anatomical landmarks such as the sphenoid bone and *falx cereberi* in B-mode echo imaging was also assessed. Images were analyzed by the same person, the first author (B.L.), who has experience in transcranial ultrasound imaging.

For each subject, the two transducer arrays were positioned approximately 2 cm superior to the bilateral temporal acoustic windows. Imaging was performed during positioning to ensure adequate contact and determine imaging field of view. Transducers were held in place using an EEG cap (Jordan NeuroScience, San Bernadino, CA). Each subject was then given a bolus injection intravenously of 10 $\mu\text{L/kg}$ followed by a 10 mL saline flush according to the Definity prescribing information. After a 30-m delay, a second bolus injection was administered to allow acquisition of additional images.

RESULTS

KLM model simulations

Results of KLM model simulations for the designed 1 MHz transducer are presented in Table 3. Figure 6 shows the simulated pulse-echo waveform and spectrum showing a center frequency of 1.08 MHz produced by transmitting and receiving into water with a single element. When this transducer is loaded with the skull and soft tissues, the KLM model predicts a decrease in SNR of 23.08 dB (inside the window) and 33.32 dB (outside of the window). For comparison, for the 1.8 MHz transducer, these figures are 38.68 (inside the window) and 43.00 dB (outside of the window).

Transducer testing

The single-element waveform and spectrum shown in Figure 7 are similar to the simulation results, although the strong harmonics do not occur in the simulation. Bandwidth is 46.86%, centered at 1.0 MHz. 50 Ω insertion loss was measured to be -58 dB. This is an improvement over the 2.3 MHz transducer (-80 dB), as the larger elements provide better electrical matching. Worst-case crosstalk on adjacent channels in the flex circuit was -46.90 dB. This improvement in crosstalk as compared to the previous 2.3 MHz transducers (-30 dB) is due to increased trace separation in the flex circuit allowed by a larger aperture (Lindsey et al. 2011). Lower cross talk in the transducer is expected to improve imaging signal to noise ratio and angular sensitivity. Element yields of the two transducers used for simultaneous imaging were 91% and 95%.

Safety measurement

Measured worst-case MI for this transducer is 0.33. Though operating at a lower transmit frequency increases MI, the output of these transducers is well below both the FDA limit and reported MIs for previous *in vivo* transcranial imaging studies (Schlachetzki et al. 2002; Holscher et al. 2005). In addition, Definity microbubbles are reported to exhibit a slight decrease in energy absorption with decreasing frequency (Chatterjee et al. 2005; Goertz et al. 2007), decreasing the potential for cavitation as compared with a transducer having the same acoustic output at a higher frequency. As we do not have sufficient voltage control to maintain constant MI across frequencies, constant transmit voltage amplitude will be maintained.

Measured worst-case value for TIC for this transducer is 1.66. As a rough comparison with a different thermal index, it may be noted that soft tissue thermal indices (TIS) of greater than 2 are often reported in the literature. Measured worst-case I_{sppa} is 2.4 W/cm² and I_{spta} is 0.068 W/cm².

Phantom imaging

The results of three phantom experiments are shown in Figure 8, in which fused renderings clearly depict flow in the expected spatial pattern at 1.2 MHz, while only the outermost legs of the tube are visible when scanning at 1.8 MHz.

In vivo imaging

In producing a 3-D rendered image, a rendering threshold must be selected below which noise is rejected and above which anatomical structures are displayed. As seen in Figure 9a, at 1.8 MHz it was not possible to determine a threshold at which intracranial structures could be visualized. However, the reduced attenuation at 1.2 MHz allows visualization of several hyperechoic structures, including the choroid plexus in the lateral ventricles and the sphenoid bone inferiorly in the coronal view of Figure 9b and the axial view of Figure 9c.

On the basis of these initial results, additional subjects were imaged outside the window using micro-bubble contrast agent according to an IRB-approved protocol as described in the Methods section.

An offline 3-D rendering of contrast-enhanced Doppler data in a single subject is shown in Figure 10. The vessels of the Circle of Willis can be seen in this image. Table 4 summarizes the detectability of arteries of the Circle of Willis in Doppler imaging and of anatomical landmarks in B-mode imaging in this study and compares with the previous 1.8 MHz study through the temporal acoustic windows. Bilateral anterior cerebral arteries are treated as a single structure, as they commonly appear in Doppler ultrasound images (Bogdahn et al. 1998; Valdueza et al. 2008). Detection rates were slightly lower than with higher frequency 3-D imaging through the temporal acoustic window, but as discussed in the Methods section (Fig. 3), imaging in this 1.2 MHz study was performed through a much more highly attenuating region of the skull.

DISCUSSION

By designing and fabricating lower frequency, large aperture matrix array probes, we have demonstrated the potential for performing 3-D transcranial ultrasound imaging not through the temporal acoustic window, but through a thicker, more highly attenuating part of the skull. This approach may be reasonably expected to enable transcranial ultrasound imaging in some patients with poor temporal bone windows. Improvement in 3-D echo imaging was significant at 1.2 MHz as compared to 1.8 MHz as seen in Figure 9. However, due to the SNR requirements for color flow imaging, microbubble contrast agent was still required.

This study merely examined feasibility and was not comprehensive given the aforementioned varying window characteristics among populations and individuals. A comprehensive study of window failure across ethnic groups and ages would provide greater insight into the prevalence of this problem, especially a study examining several different transmit frequencies.

Detection rates of middle cerebral and internal carotid arteries were slightly lower when imaging outside the window at 1.2 MHz as compared to imaging through the temporal acoustic window at 1.8 MHz in the previous study (Lindsey et al. 2011). Nonetheless, to our knowledge, transcranial ultrasound imaging outside of the temporal acoustic window has not been demonstrated previously. Two of five subjects exhibited a partial or complete unilateral failure to image, suggesting window failure will persist in some subjects even at a lower frequency; Figure 3 suggests this occurs when the skull becomes too thick on one side. Both of these subjects were, however, successfully imaged through a single side. An example of single-sided imaging failure is shown in Figure 11. Conversely, for subjects having adequate windows, reduction in transmit frequency would still increase penetration, improving the ability to image contralateral structures.

The presented results suggest that a large, low-frequency (~1 MHz) array may allow imaging outside of the window, which would prove helpful both for imaging subjects with poor acoustic windows and for allowing operators with minimal training to image subjects from an ambulance or other field setting. In a small study, the ability to detect blood flow in internal carotid and middle cerebral arteries in healthy volunteers is encouraging, especially when one considers that 68% of strokes affect the anterior circulation, and of these 96% occur in the middle cerebral arteries (Bogousslavsky et al. 1988).

In particular, this study only examined healthy individuals; as such, the ability to image blood flow in pathologic states such as low flow velocity or compensated flow in the event of a stroke remains unknown. In addition to the ability to image an occlusion as a distinct

absence of blood, any technique for diagnostic imaging of stroke must also be able to rule out intracerebral hemorrhage. While some encouraging results have been published using ultrasound (Meyer-Wiethe et al. 2009), ultrasound imaging techniques have yet to demonstrate this capability in a large clinical trial.

Designing a large aperture produces beams which are virtually identical to 2.3 MHz simulations (−6 dB beam width of 3.6 mm at 2.3 MHz as compared to 3.8 mm at 1 MHz) (Lindsey et al. 2011). When using a large aperture, individual elements are more likely to encounter varying aberration and attenuation due to the inhomogeneity of the skull. However, these effects are diminished by the lower frequency of the waves. In the future, heating at the probe surface could become a concern due to energy deposition at the skull's outer surface. However, because a probe with a large surface area spreads out energy, switching to a large array at the same power setting is thus less of a concern than increasing the transmit power when using a small array.

We have presented a system for overcoming temporal acoustic window limitations in transcranial ultrasound imaging which relies on a bilateral approach using low frequency, large aperture sparse arrays. It is our hope that when combined with recent developments in portable ultrasound, such an approach may be useful to allow acquisition of useful images either in individuals with poor windows or outside of the temporal acoustic window in the field.

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Fig. 1. (a) Array placement over both temporal acoustic windows, and (b) volume acquired by each array during such a scan, with a steerable Doppler beam shown in blue.

Fig. 2.

Three-dimensional contrast-enhanced (Definity) renderings acquired from scanning two different healthy volunteers (both 24-y-old females) with 2.3 MHz echo and 1.8 MHz Doppler according to an IRB-approved protocol. Subject (a) had significantly more favorable windows than Subject (b), in which the major cerebral arteries appear small and Doppler signal dropout is apparent. MCA = middle cerebral artery; ICA = internal carotid artery.

Fig. 3. Predicted system SNR as a function of skull thickness when scanning both inside and outside of the temporal acoustic window.

Fig. 4.

(a) Aperture design for 1 MHz sparse matrix array. Gray elements only transmit; white elements both transmit and receive. Simulated two-way response of this aperture (b) on-axis, (c) steered to $+16^\circ$ in both azimuth and elevation and (d) steered to $+32^\circ$ in both azimuth and elevation.

Fig. 5.
(a) Photograph and (b) micrograph of an array after dicing. Gold pads extending beyond the PZT in (a) are extra pads used only for alignment. Element pitch is 0.725 mm.

Fig. 6. Simulated pulse-echo impulse response (a) and spectrum (b) for a single element using PiezoCAD. The units on the ordinate axes are measured output voltage (V_o) relative to applied input voltage (V_i).

Fig. 7.

(a) Typical single element pulse-echo response and (b) average spectrum from all single-element acquisitions. The simulated spectrum of Figure 6 is reproduced for comparison (dashed line).

Fig. 8. Results of three separate tests of water tank flow testing in the presence of 3 mm Wallgone rubber using two different sets of transducers at the indicated frequencies. Attenuation is 28.8 dB at 1.2 MHz and 43.2 dB at 1.8 MHz. Images are acquired at the same transmit voltage.

Fig. 9.

Fused renderings of the same subject using the described 1.8 MHz (a) and 1.2 MHz (b and c) imaging system. Coronal views are shown in (a) and (b) and an axial view in (c). Both data sets were acquired outside of the temporal acoustic window. For 1.8 MHz imaging, we were unable to find a threshold setting which allowed visualization of anatomical structures. In the 1.2 MHz image, anterior horns of lateral ventricles, sphenoid bone and contralateral skull surfaces are visible.

Fig. 10.

Registered, fused rendering of a healthy 34-y-old male with Definity microbubble contrast enhancement. ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery.

Fig. 11.

An example of unilateral imaging failure in one subject, a 32-y-old African-American male. Imaging with the low frequency array does enable imaging through the right side of the subject's skull outside of the temporal acoustic window, but not through the left side. ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery.

Table 1

Comparison of window failure rates in previous transcranial ultrasound studies

Study	Number of subjects	Study location	Transmit frequency	2-D imaging or 1-D TCD	Window failure rate
Hashimoto et al. 1992	423	Japan	2.0 MHz	1-D TCD	29%
Seidel et al. 1995	84	Germany	2.5 MHz	2-D imaging	20%
Baumgartner et al. 1997	33	Switzerland	2.0–2.5 MHz	2-D imaging	34% (with contrast agent)
Marinoni et al. 1997	624	Italy	2.0 MHz	1-D TCD	8%
Postert et al. 1997	172	Germany	2.25 MHz	2-D imaging	12%
Hoksbergen et al. 1999	112	The Netherlands	2.0–2.5 MHz	2-D imaging	11%
Gahn et al. 2000	171	Germany	2.0–2.5 MHz	2-D imaging	29%
Krejza et al. 2007	90	United States	2.0 MHz (1-D TCD) 2.5 MHz (2-D imaging)	Both	11% (both 1-D TCD and 2-D imaging)
Wijnhoud et al. 2008	186 (stroke patients)	The Netherlands	2.0 MHz	1-D TCD	18%

Table 2

Materials parameters for KLM model simulations

Material	Z_0	Thickness	α (attenuation)
PZT-5H (TRS HKI-HD)	26.95 MRayl	1.37 mm	—
Extracranial Tissues	1.54 MRayl	5 mm	1 dB/cm/MHz
Skull (inside window)	4.70 MRayl at 1.2 MHz 4.43 MRayl at 1.8 MHz	3 mm	2.8 dB/cm/MHz
Skull (outside of window)	4.38 MRayl at 1.2 MHz 4.06 MRayl at 1.8 MHz	4 mm	20 dB/cm/MHz
Brain	1.54 MRayl	140 mm	1 dB/cm/MHz

Table 3

Results of KLM modeling, 1.2 MHz excitation response

	Without skull	With skull (within window)	With skull (outside of window)
Pulse-echo amplitude relative to no skull case	0 dB(reference)	−23.08 dB	−33.32 dB
Center frequency (f_0)	1.08 MHz	1.07 MHz	1.00 MHz
−6 dB bandwidth	32.89%	28.31%	16.61%

Table 4

Detection rates of major cerebral arteries through the acoustic windows in 3-D Doppler imaging at 1.8 MHz (Lindsey et al. 2011) versus outside the acoustic windows at 1.2 MHz

Doppler scanning frequency	Probe placement	Detection rates				Echo landmarks
		ACA	ICA	MCA	PCA	
1.8 MHz	Within temporal acoustic windows	1/4	8/8	8/8	6/8	4/4
1.2 MHz	Outside of acoustic windows	4/5	8/10	9/10	3/10	8/10

ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery.